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Special Report

Advancing Laboratory Medicine through Innovation: A Tale of Six Inventors

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"Discovery consists of seeing what everybody has seen and thinking what nobody has thought." Albert von Szent-Gyorgy (Nobel Prize in Physiology or Medicine, 1937)

In a recent issue of *Science Translational Medicine (1)*, Yock and colleagues of Stanford University discuss the merits and challenges of developing a discipline of medical technology innovation. Innovation is defined as "inventiveness put to use"; a discovery that results in a commercial product or service. In this provocative article, the authors discuss two main streams of educational theory and practice that together form the basis for teaching innovation: design thinking and entrepreneurship education (Fig. 1). Design thinking focuses on identifying the opportunity and need, developing the idea to solve the problem, building the prototype, and testing the product, while entrepreneurship education provides an introduction to the skills and approaches required to take a product or a service and successfully commercialize it. The authors argue that medical technology innovation is the ideal environment for interdisciplinary team building combining physicians, engineers, scientists, and business professionals.

In laboratory medicine, numerous scientists and physicians have been able to successfully launch their inventions into the marketplace; inventions that changed the practice of medicine. Six of those inventors were invited to share their success stories with the readers of *Clinical Chemistry*. How did they do it? What influenced most their success? What were the major drivers for their pursuits? Did they have formal training in the innovation process? In addition, they were asked to score, in terms of relevance, 20 factors that influenced their endeavors (Fig. 2).

My Personal Journey in Laboratory Medicine Innovation: From Industry to Academia. Eleftherios P. Diamandis

There is no single recipe for success in innovation and there is a myriad of examples of highly successful entrepreneurs who have not taken a single course in entrepreneurship. I will summarize some of my own experiences as a scientist and innovator and comment on competencies that I acquired.

I believe that the cornerstones to my apparent successes were my undergraduate degree in chemistry (1976) and my PhD in analytical chemistry (1979). This training made me an analytical biochemist, versatile in the art of quantitative measurements. These skills were complemented nicely with my postdoctoral training in clinical chemistry (1982–1984) and my medical degree (1986).

My desire to return from Greece to Toronto as a professional was hampered by the Canadian immigration laws of that time, which stipulated that recruitment of foreign individuals must be sponsored by companies that needed unique skills. Although at that time I was concerned about working in industry, I had no choice but to accept a position as director of research and development of a small biotechnology company, CyberFluor, in 1986. CyberFluor was interested in developing highly sensitive nonisotopic immuno-

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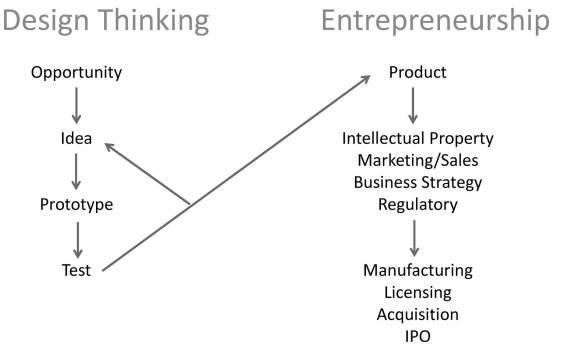


Fig. 1. Components of innovation as suggested in a recent review on biomedical technology innovation as a discipline [Yock et al. *(1)*].

Design thinking encompasses the creative roadmap toward innovation, including awareness of the opportunity or unsolved problem, an idea to fill the opportunity, development work to design and prototype the solution, and experimental testing as a reality check. Multiple cycles of ideas, prototyping, and testing may be required before a viable product emerges. Entrepreneurship assesses the feasibility of commercializing the product, including components of uniqueness (intellectual property) and market potential. Regulatory requirements and business strategy often suggest outcomes that may include in-house manufacturing, licensing, mergers/acquisitions, or an initial public offering (IPA).

logical assays for clinically relevant analytes. At that time, I committed to a 2-year tenure, in exchange for landed immigrant status. I did not realize then that the 2 years I spent at CyberFluor were probably the most important of my career. Working in an industrial environment and overseeing eight PhD scientists, I had the advantage that the project/problem identification was already made for me. It was a very specific project, with a very specific target outcome; that is, to develop an instrument that could measure time-resolved fluorescence originating from lanthanide chelates *(2)*. When I joined, I took on the challenge of working with engineers, programmers, physicists, and others to perfect the instrument prototype. At the same time I initiated a program to optimize the reagents through novel conjugation techniques *(3–5)*. In the end, we put together a combination of instrument/reagents, a product that was marketed successfully in Canada and abroad. Without my realizing it at that time, my knowledge in Analytical Biotechnology and Laboratory Medicine was highly enriched with other skills of entrepreneurship, including intellectual property protection, technology transfer, marketing, production and quality control, fundraising, investor relations, and financing. I am not sure if I could have ever obtained such diverse training, in such a short time, in any university program.

Despite my leaving industry in 1988 to return to academia, the knowledge that I acquired was invaluable and has followed me in my current career as a scientist. I did not cut ties with the company but, rather, I became the chair of their scientific advisory board. I established relationships between my new employer (University of Toronto and affiliated hospitals) and CyberFluor, which resulted in the continuation of my research in areas of interest to CyberFluor in exchange for research funds. A major boost was the fact that such contributions were matched dollar for dollar from provincial or federal sources. Over the following 20 years, matching funds have been the cornerstone of my research budget.

When CyberFluor was acquired and eventually closed, I used my skills to identify other commercial sponsors that provided major funding for our research programs in exchange for intellectual property. My strengths in quantitative analytical biochemistry were adapted to solving other problems in laboratory medicine, such as identification and validation of diagnostic and prognostic biomarkers for various diseases, including cancer. This is a well-defined unmet clinical need with applicability to patient care. The clear biomedical question, with commercial potential, attracted many companies to work with us. My current academic employer has a very strong technology transfer office that facilitates discussions and signs deals with prospective collaborative companies. My deep understanding of what industry wants from us, and what we need from them, facilitated the development of successful relationships and attraction of substantial research money. Contrary to the view that companies may interfere with the freedom of research in academia, my experience has been the opposite. We have always defined our research and found companies with matching interest, not the other way around. More recently, we opened up new areas based on our core competencies in quantitative analytical chemistry. We apply mass spectrometry–based proteomic approaches for novel biomarker identification *(6, 7)*. These programs are flourishing with both industrial as well as other funding, because they are attempting to address a very clearly defined clinical need.

Hospitals are highly supportive of collaborative relationships with industry for many reasons, including overhead income, covering of patent costs by industry, licensing fees, and partial ownership of spin-off companies.

Other benefits of industrial sponsors participating in academic research include training graduate and postdoctoral students in industrial environments and teaching them how these relationships can be initiated, sustained, and expanded.

My own path to becoming an innovator was initiated by a series of uncoordinated steps early in my scientific career. Collaborations with industry can help sharpen the focus of one's research to identify problems that require solutions and lead to new products, attract new and matching funding, and train highly qualified personnel in academic and industrial environments, and can lead to licensing agreements, spin-off companies, patents, and generation of new income through licensing. As mentioned earlier, there is no single recipe to becoming a successful innovator and the route that I chose appears to best fit my own inspirations and desires. I hope that this commentary will be a case study for young clinical chemists who are seeking to become innovators in laboratory medicine.

Innovation at the Convergence of Opportunities.
Y.M. Dennis Lo

I spent the early part of my academic career at the University of Oxford but decided to return to my home city, Hong Kong, in 1997. This career move prompted me to consider exploring a new research direction. Two reports on tumor-associated genetic alterations in the plasma and serum of cancer patients at the end of 1996 *(8, 9)* inspired me and my coworkers to see if a fetus would also release its DNA into the plasma and serum of its pregnant mother. This work led to the discovery of the presence of cell-free fetal DNA in maternal plasma and serum *(10)*. We were able to show that one could determine a variety of fetal genetic characteristics by maternal plasma/serum DNA analysis, and were granted our first patent on this technology.

Initially, we focused on the detection of paternally inherited genetic sequences that were absent in the pregnant mother's genome, e.g. the Y chromosome of a male fetus or the *RHD* gene of a rhesus D-positive fetus. Such tests are now in use in a number of centers for the prenatal diagnosis of sex-linked diseases, congenital adrenal hyperplasia, and fetal *RHD* genotyping. We then embarked on the challenging task of attempting to detect a fetus with trisomy 21 by using maternal plasma. This task is very demanding technologically because fetal DNA represents only a minor proportion of the DNA present in maternal plasma *(11)*. Over the next 10 years, we investigated multiple approaches to achieve this goal, including those based on plasma RNA analysis *(12)* and DNA methylation analysis *(13)*. In 2007, we reported an approach based on single DNA molecule counting *(14)* and showed in 2008 that massively parallel sequencing was an effective way for implementing this concept *(15)*. We recently completed a large-scale validation study that shows the robustness of this approach *(16)*. We have just seen the launch of this technology in the US and are anticipating clinical adoption in a number of other countries in the near future.

A number of factors have enhanced my ability to push forward in this field. First, my move from Oxford to Hong Kong had created an opportunity whereby I was more receptive to taking risks in my research direction than I might have been had I not moved my career from one continent to another, which is inherently risky in itself! The field of noninvasive prenatal diagnosis was filled with uncertainties at the end of the 1990s because decades of research had not resulted in a robust method for the isolation of fetal cells from maternal blood. The jump from targeting fetal cells to analyzing cell-free fetal DNA might be regarded by many as even riskier because many researchers did not believe that the new approach would yield precise fetal chromosome dosage information.

Second, I am fortunate enough to be able to work with an excellent team, especially Rossa Chiu and Allen Chan, both within my department, and have collaborated with a dedicated team of obstetricians who have provided the clinical input and samples for the research.

Third, I was able to gain access to new technologies at key time points in my career. The first such technology was real-time quantitative PCR, which was crucial for the accurate measurement of fetal DNA concentrations in maternal plasma *(11)*. The understanding of these quantitative parameters had been essential for the subsequent development of trisomy 21 testing using plasma nucleic acids. The second such technology was mass spectrometry for nucleic acid analysis, which allowed us to show for the first time that plasma nucleic acids could be used for the direct elucidation of fetal chromosome dosage information *(12, 13)*. The third such technology was massively parallel sequencing, which allowed us to realize a general and robust approach for detecting fetal chromosomal aneuploidies using molecular counting *(15)*.

I have also been fortunate to have access to the necessary funds for supporting my research. The Inno-

vation and Technology Fund of the Hong Kong SAR Government and the Areas of Excellence Scheme of the University Grants Committee have provided the much-needed support for my work. A large donation from the Li Ka Shing Foundation in 2005 allowed the establishment of the Li Ka Shing Institute of Health Sciences and my appointment as the founding director. The Institute has provided state-of-the-art research facilities that have allowed my team to compete effectively.

A good commercial partner has also been important for my efforts in realizing noninvasive prenatal diagnosis. A chance encounter with Charles Cantor, the Chief Scientific Officer of Sequenom, at a conference in Thailand in 2002, resulted in such a link. Since then, we have been collaborating both on the scientific *(12, 14, 15)* and the commercialization aspects of the technology.

In summary, my research has been facilitated by the chance convergence of many favorable conditions. I hope that my story and those of other technological innovators might help the creation of institutional or funding infrastructures that would improve the odds of encountering such a convergence.

Innovation on Two Continents.
Peter Wilding and Larry J. Kricka

This is the story of two disparate individuals who have forged separate, but similar, careers, often working together for years developing technology. One likes to sing and play golf, the other (L.J. Kricka) lifts weights and writes alliterative prose. The early stages of their careers differ greatly but they share a love for innovation.

One of us went straight to university after high school, whilst the other (P. Wilding) entered the clinical laboratory as a 17-year-old technician and was soon conscripted into the army as a medical technologist in a military hospital and learned all the basic elements of hospital pathology, including autopsies, before reaching the age of 21. Realization that a meaningful career would require higher qualifications led both of us to doctoral degrees, in clinical enzymology (P. Wilding) and chemistry (L.J. Kricka).

We both broadened our experience and 1972 found us as colleagues at the Wolfson Research Laboratories in the Queen Elizabeth Medical Centre of the University of Birmingham, UK. This laboratory, headed by a legendary clinical chemist, Prof. Tom Whitehead *(17)*, was unique in the UK as it was funded by the university and the UK Department of Health to develop, evaluate, and use new automated methods for use in routine laboratories. It included a well-equipped mechanical and electrical engineering facility employing engineers and tool-makers, a state-of-the-art computer facility, and the latest commercial instrumentation to meet routine clinical service demands in the medical center. It also had arranged specific access to patent agents to facilitate patent filings. For both of us, this experience was the basis of much of our future success as we learned that multidiscipline teams, directed by bold management, can lead to enormous progress.

We were involved with two major projects at the Wolfson, both of which were commercialized. These were the automated analyzer sold by Coulter as the DACOS, which played a large role in influencing the migration from continuous flow analysis (autoanalyzers) toward discrete systems (P. Wilding) and enhanced chemiluminescence (L.J. Kricka) that was applied in immunoassay and blotting products (e.g., Amerlite) *(18, 19)*.

One of us continued in academic life, and the other (P. Wilding) went on to work in the diagnostics industry, firstly as a director and vice president of diagnostics with the Technicon Corporation and then as a vice president of research and development with the SmithKline Beckman Corporation. The experiences gained during this period proved invaluable later when developing new technology in academia. It also instilled a great appreciation of the complexity, and diligence, necessary to develop a new technology and bring it to market.

By 1987 we were once again colleagues, this time in the Department of Pathology and Laboratory Medicine at the University of Pennsylvania Medical Center in Philadelphia, and a new era of technology opened for both of us.

We had both been developing a growing fascination with "micro-technology" and we quickly developed a collaborative effort with the University of Pennsylvania Engineering School and Prof. Jay Zemel, a distinguished electrical engineer. Within a year we had developed our first microfluidic micro-

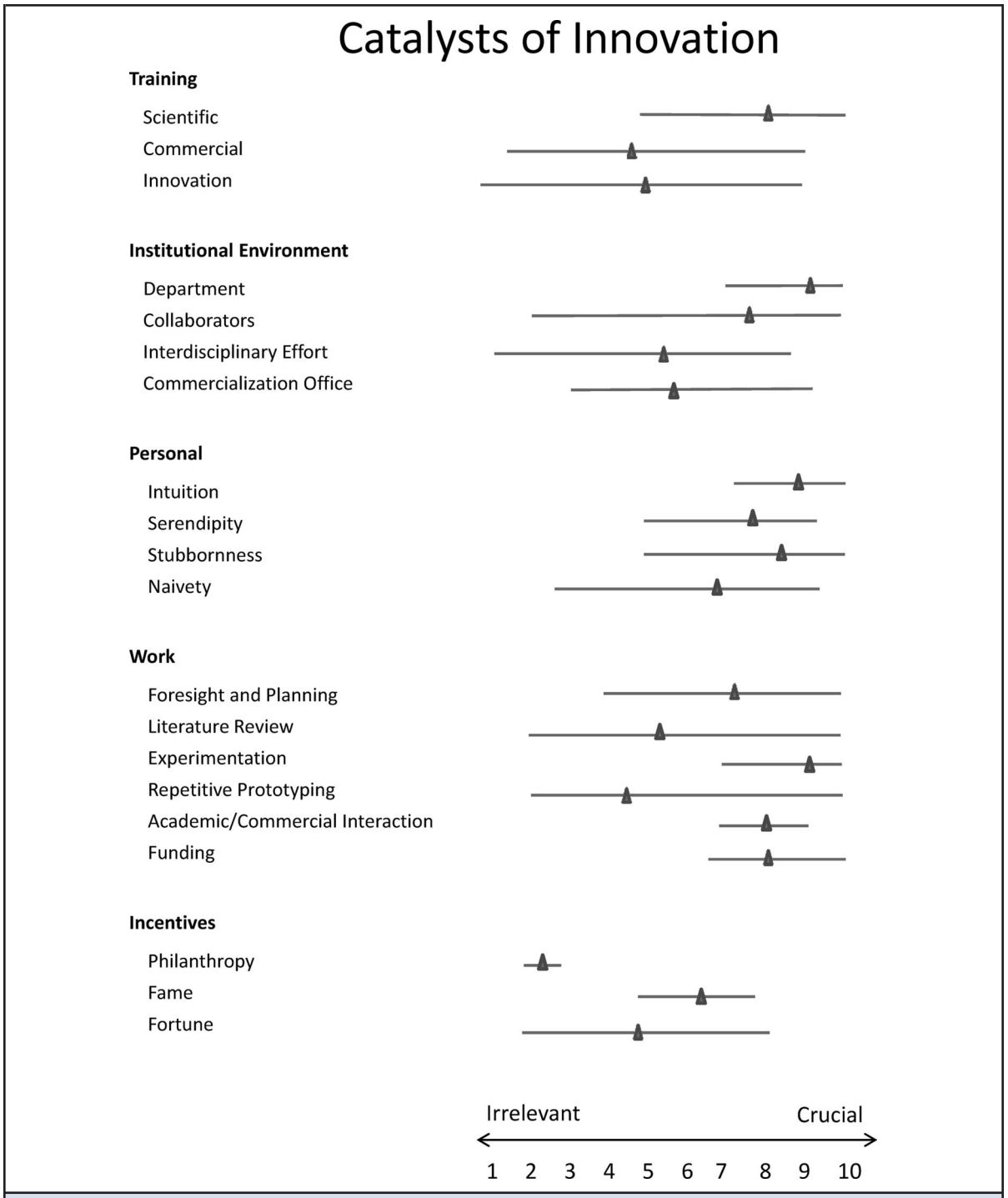


Fig. 2. The importance of training, environment, personal, work, and incentive factors for innovation.
Each of the 6 inventors highlighted here ranked 20 factors from irrelevant [Yock et al. *(1)*] to crucial [Lo et al. *(10)*]. For each factor, the median response is shown as a triangle with the range indicated as a line.

chip with simple channels etched in silicon with glass covers that facilitated observation and filming during experiments. In 1988, there was little information about the behavior of blood in microchannels and we set about documenting these phenomena *(20, 21)*.

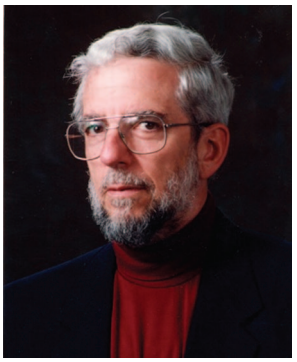
Our excitement at being able to construct and use microfluidic chips was contagious, and we soon built a list of potential applications for the microchips (guided by our roles as clinical laboratory directors). It rapidly became apparent that the work involved intellectual property that should be patented. This process was aided by the fact that the University of Pennsylvania had a well-developed system for filing invention disclosures through its Center for Technology Transfer. However, work of this type, especially if it is to be patented, needs financial support. Efforts to gain support from the NIH were rebuffed as "too much engineering," whereas approaches to the National Science Foundation generated concern over "too clinical an approach."

Progress past this point and acquisition of the funds to hire staff and file the patents were achieved through perseverance, enthusiasm about the project, and help from former colleagues who had deserted diagnostics for roles as venture capitalists. We quickly learned that it was important to be able to communicate the benefits and the commercial potential of new technology if we were to succeed in gaining support for our work. A few years later, when patents had been filed and we were starting to publish our work, we spent many hours selling our ideas to prospective sponsors. Nearly all that effort was in vain, but we persisted and eventually raised $1.5 million and formed a fledgling company ChemCore together with the University. The company soon merged to become Caliper Technology Corp and a successful biotech company was born.

During this time we recruited a team that explored numerous applications of our chips, particularly sperm analysis and polynucleotide amplification, especially PCR. The small team we built during that period still communicates and stays friends, but we have all learned that innovation needs a willingness to try "off beat" ideas, to be persistent, to exploit serendipity, to patent first and publish later (!), to value your colleagues, and to work in an institution where freedom to explore new boundaries is encouraged.

The work on microfludic devices has resulted in 22 US patents and generated over $20 million, to date, for the University of Pennsylvania. Money was the consequence—it was never the motive!

Innovation: Solving an Unmet Need.
Jack H. Ladenson



Some aspects of my career, including the development of antibodies and assays for markers of cardiac injury, have already appeared *(22–26)*. I will try not to repeat most of it here.

I was a "late bloomer" with a lackluster career as an undergraduate at Pennsylvania State University. Following college, I spent a few months trying to make a living as a professional gambler but it did not work and I spent a year on and off on active duty with the Air National Guard. While on active duty, I took stock and decided to try to pursue a graduate degree in chemistry. I was accepted as a "special student" at the chemistry department of the University of Maryland and then as a full graduate student in analytical chemistry the next semester. While there, I had to prove my suggested thesis project was impossible. This experience was very instructive and eventually I showed that electrochemical generation of the Ag^{++} ion (a very powerful oxidate) still could not react with creatinine (Bill Purdy's laboratory was funded to develop electrochemical biological methods) and then formulated my own project. Upon graduation I had a number of job opportunities because postdoctoral fellowships were not common in analytical chemistry. None excited me but I heard a talk on clinical chemistry by Donald Young, then at NIH, that did. I went to Hartford Hospital as the first postdoctoral fellow in clinical chemistry with George Bowers, Jr., and Bob McComb and worked on a project concerning free (ionized) calcium, during which I had to make my own electrodes. After joining the division of laboratory medicine at Washington University, I continued working with activity measurements via electrode and then switched to antibody and assay development in the 1980s. This was successful due to having a brilliant collaborator, Dave Dietzler, and a talented congenial laboratory team, e.g., Vonnie Landt, Sharon Porter, Hem Vaidya, Geza Bodor, and Dave Silva.

The work on cardiac markers started with an unmet practical need. The assays for CK-MB were too slow for the clinical requirement. Once this problem was solved, my feeling was satisfaction and not some of the other incentives (Figure 2), some of which evolved later. Following patenting and the release back to the University of licensing rights by Monsanto, Duke Leahey (then the only individual in technology management) and I went through a learning curve together about the nuisances of how to get the technology to the field. Publication of information is very useful but I

learned that getting it to become a useful product takes considerable additional effort. After a year or so I elected not to form a company but to license the technology. I also negotiated with my department about possible uses of royalties it might obtain.

The development and licensing of additional useful cardiac markers allowed me to pursue efforts in improving Laboratory Medicine in developing countries and to endow some chairs and scholarships, but this was something that evolved and was not the motive behind the original work, which was developing rapid and specific blood tests for the common clinical problem of suspected "heart attack."

This type of innovation used to be common to all hospital clinical chemists who had to adapt procedures to the continuous flow autoanalyzer technology that was dominant when I entered the field. With the advent of closed systems and greater regulation, such innovation in the general hospital has become difficult. However, in the right university environment, I believe it still can flourish. I recall a statement I read years ago: "I have sometimes thought of the modern university as a series of individual faculty entrepreneurs held together by a common grievance over parking" by Clark Kerr, President of the University of California System, 1963 Godkin Lectures at Harvard *(27)*.

I believe innovation and entrepreneurship are natural offshoots of scientific efforts to solve unmet needs and acquire new information about disease and cellular function. However, the environs where innovative work can be done are probably changing, e.g., academic rather than general hospital; small or start-up company rather than large in vitro diagnostic company.

I do not know if there is one set of characteristics or training that can lead to success, but I know there is the ability to recognize the potential for success. For example, the same individual hired three of the six people who were invited to partake in this article (probably would have tried to hire the others if he knew of them). Leonard Jarett hired me at Washington University and Peter Wilding and Larry Kricka after he went to the University of Pennsylvania.

Monogamous Entrepreneurship through Evolution. Carl Wittwer

I never considered commercialization a respectable goal. As an academic, my first job as an assistant professor at the University of Utah (1988) included a mandate to identify new technologies that might become important to our fledgling reference laboratory, Associated and Regional University Pathologists. PCR was a new research technique, and the introduction of a thermostable polymerase suggested the possibility of automation by thermal cycling. However, at the time you couldn't buy a thermal cycler, and PCR was tedious to perform manually. So tedious that it led to several grant proposals (all rejected) and some prototypes based on hair dryers and capillary tubes. These simple, "Rube Goldberg," prototypes performed PCR in 10–15 minutes, over 10-times faster than the current state of the art *(28)*.

Teaming up with a business savvy Renaissance man (Kirk Ririe), we licensed rapid cycling from the University and formed Idaho Technology, sharing space with Kirk's family business that made replacement parts for potato harvesters. Surviving on sales of the niche product, the RapidCycler®, for a few years, our first break was a Small Business Technology Transfer grant from the NIH to combine rapid cycling with fluorescence interrogation. Borrowing the optics from a flow cytometer, we built the prototype LightCycler® in 1996, introducing rapid cycle PCR, dual hybridization probes, SYBR Green I, and melting analysis to real time PCR *(29)*. In 1997, LightCycler technology was licensed to Roche in most fields, who launched the product worldwide the next year. The US Air Force funded a field-hardened version with automatic detection, leading to the Joint Biological Agent Identification and Diagnostic System contract in 2004, providing the US Government's first line of defense against biologic weapons, a program that continues today. The first genetic tests to be FDA approved were obtained on the LightCycler in 2002 and were based on assays developed at Associated and Regional University Pathologists in 1996 *(30)*, and several biothreat agents as well as influenza are now FDA approved.

A deliberate focus on improving melting analysis resulted in high-resolution melting in 2003 *(31)*, leading to commercial release of LCGreen® dyes and the LightScanner®. High-resolution melting is now accepted as the best genetic scanning technique and the simplest method of genotyping without labeled probes, leading to broad licensing in the field. Analysis of complex loci was further enabled by melting analysis with LCGreen using unlabeled probes *(32)* and later snapback primers *(33)*. Melting analysis has become so powerful that it has supplanted real time PCR in the FilmArray®, a multiplex diagnostic device FDA approved for upper respiratory infections in 2011.

Idaho Technology is now a 300-person company. One third of its income comes as royalties from the technologies mentioned above. I maintain my academic laboratory at the University of Utah. Our academic/company marriage has evolved into one of mutual respect and synergistic use of our differences. In the end industry is motivated by profit, not scientific

quality or accuracy. Competition in the PCR field has decreased instrument cost. However, little progress has been made in matching temperature cycling to the biochemical requirements of PCR. As an academic, I continue to focus on better temperature control to improve PCR and melting analysis (www.dna.utah.edu), hoping for better assays based on simple principles.

Conclusion

As the stories of these six inventors demonstrate, there is more than one path to success. Some started their careers on one continent and moved to another, some worked only in academia while others also in industry, and only a few had commercial and innovation training. The perceived value of the catalysts that led to their inventions differed greatly for some elements but only slightly for others (Fig. 2). They believed that the department in which they worked was crucial to their success because it provided the needed facilities, the potential mentoring, the intellectual camaraderie, and the freedom to pursue. Almost equally highly ranked was Experimentation: how to design, execute, confirm, and interpret the experiment to determine the likelihood of success. The next two highest scores belonged to Intuition and Stubbornness; the inventors believe that if you do not have a strong intuition, you cannot invent, and if you are not stubborn enough, you cannot persevere. Funding and Academic/Commercial Interaction, the two most crucial, practical, and needed logistics to succeed and reach the final goal were highly ranked as well. We hope that these stories inspire young scientists and clinicians in Laboratory Medicine to look beyond the obvious, connect seemingly unconnected things, question established norms and practices, and strive to create better technologies and tools with the hope of improving healthcare for mankind.

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